FORM PTO-1390 (REV. 12-2001) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 2000.551 US

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): To be assigned 10/089542

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP01/04069	04-April-2001	05-April-2000

TITLE OF INVENTION: DRUG COMBINATION FOR THE TREATMENT OF HEADACHE COMPRISING A NON-STERIODAL ANTI-INFLAMMATORY DRUG

APPLICANT(S) FOR DO/EO/US: NICKOLSON, Victor

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. [X] The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is attached hereto (required only if not communicated by the International Bureau).
   b. [X] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. [ ] is attached hereto.
   b. [ ] has been previously submitted under 35 U.S.C. 154(d)(4).
7. [XX] Amendments to the claims of the International Aplication under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [XX] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. [XX] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] An English lanugage translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [XX] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [XX] A FIRST preliminary amendment.
14. [ ] A SECOND or SUBSEQUENT preliminary amendment.
15. [ ] A substitute specification.
16. [ ] A change of power of attorney and/or address letter.
17. [ ] A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. [ ] A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. [ ] A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. [ ] Other items or information:

Express Mail EL 839703497 US

U.S APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
To be assigned	PCT/EP01/04069	O 2000.551 US

21. [XX] The following fees are submitted:

	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1040.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$740.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	12 - 20 =		x **$18.00**	$	
Independent claims	3 - 3 =		x **$84.00**	$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$280.00**	$	
TOTAL OF ABOVE CALCULATIONS =				$	
[ ] Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2. +				$	
SUBTOTAL =				$	
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
TOTAL NATIONAL FEE =				$	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$ 40.00	
TOTAL FEES ENCLOSED =				$	
				Amount to be refunded:	$
				charged:	$ 930.00

a. [ ] A check in the amount of $ _____ to cover the above fees is enclosed.

b. [XX] Please charge my Deposit Account No. 02-2334 in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [XX] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2334 A duplicate copy of this sheet is enclosed.

d. [ ] Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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45,825
REGISTRATION NUMBER

Attorney Docket Number O 2000.551 US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:

NICKOLSON, Victor

Serial Number: To be assigned Group: To be assigned

Filed: Concurrently herewith Examiner: To be assigned

For: DRUG COMBINATION FOR THE TREATMENT OF HEADACHE COMPRISING A NON-STERIODAL ANTI-INFLAMMATORY DRUG

PRELIMINARY AMENDMENT

Honorable Commissioner of Patents
Washington, D.C. 20231

March 29, 2002

Sir:

Prior to the calculation of the fee in the above-identified application, Applicants respectfully submit the following amendments:

In the Claims

Please cancel claims 4-8 without disclaimer or prejudice to the subject matter contained therein.

Please amend the claims as follows:

1. (Amended) A pharmaceutical composition, comprising:

paracetamol or a non-steroidal anti-inflammatory drug, or a pharmaceutically acceptable salt or solvate thereof,

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mirtazapine, or a pharmaceutically acceptable salt or solvate thereof, and

optionally in association with one or more pharmaceutically acceptable carriers.

2. (Amended) The pharmaceutical composition according to claim 1, wherein said non-steroidal anti-inflammatory drug is selected from the group consisting of aceclofenac, antipyrine, acetylsalicylic acid, benoxaprofen, butibufen, caprofen, celecoxib, diclofenac, dipyrone, etodolac, flosulide, flurbiprofen, FR 140423, ibufenac, ibuprofen, indomethacin, ketoprofen, ketorolac, lornoxicam, loxoprofen, lysine clonixinate, M-5011, meclofenamic acid, meloxicam, metiazinic acid, nabumetone, naproxen, NS-398, numesulide, oxyphenbutazone, D-penicillamine, phenylbutazone, piroxicam, pyrazolone, rofecoxib, salsalate, salicylate, SC-58236, SC58560, sulfasalasine, sulindac, tiaprofenic acid, tenidap, tenoxicam, tepoxalin, tolfenamic acid, tolmetin and zaltoprofen.

3. (Amended) The pharmaceutical composition according to claim 2, wherein said non-steroidal anti-inflammatory drug is ibupofen.

9. (Amended) A method for treating a headache in a subject, comprising:

administering to said subject an effective amount of mirtazapine in combination with paracetamol or a non-steroidal anti-inflammatory drug.

10. (Amended) A method of treating a headache in a subject according to claim 9, wherein the amount of mirtazapine is between 0.1 and 5 mg.

11. (Amended) The method of treating a headache in a subject according to claim 9, wherein the headache is a tension-type headache.

12. (Amended) A patient pack for the treatment of a headache, comprising:

means for administration of metered dose units in combination with packaging material suitable for said dose units, wherein the patient pack comprises mirtazapine, and paracetamol or a non-steroidal anti-inflammatory drug, and optionally, said packaging material is including means to help a recipient using the dose units most suitably for the treatment of a headache.

13. (Amended) The patient pack according to claim 12, wherein the dose units comprise pharmaceutical auxiliaries and mirtazapine in an amount between 0.1 and 5 mg.

Please add the following claims:

--14. A method of treating a headache in a patient, comprising:

administering an effective amount of the pharmaceutical composition according to claim 1.

15. The method according to claim 14, wherein the effective amount of the pharmaceutical composition comprises about 0.1 to 5 mg of mirtazapine.

16. The method according to claim 14, wherein the headache is a tension-type headache.

17. The method according to claim 14, wherein the effective amount of the pharmaceutical composition comprises about 0.1 to 5 mg of mirtazapine and wherein the non-steroidal anti-inflammatory drug is ibuprofen.--

REMARKS

Applicants have canceled claims 4-8. Applicants have added new claims 14-17. Upon entry of the above preliminary amendment, claims 1-3 and 9-17 will be pending. Claims 1, 9, and 12 are independent claims.

Applicants have amended claims 1 and 3 to clarify the subject matter and to conform to U.S. patent practice. The specification

on page 2, line 30 to page 3, line 9 provides support for the amendment to claim 2. Applicants have amended claims 9 and 12 to conform to U.S. patent practice. Applicants have amended claims 10, 11, and 13 to correct dependency and subordinate claims to independent claims 9 or 12.

New claims 14-17 find support in original filed claims 1-3 and claim 9. Applicants have not raised any issue of new matter.

Conclusion

Applicants respectfully submit that the present application claims patentable subject matter and is in condition for allowance.

Attached hereto is a marked-up version of the changes made to this application by this Preliminary Amendment.

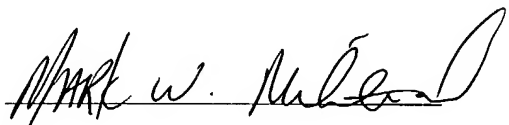
If the Examiner believes for any reason that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (302) 934-4395, in Millsboro, Delaware.

If necessary, the Commissioner is hereby authorized in this, concurrent, and further replies, to charge payment or credit any

Attorney Docket Number O 2000.551 US

overpayment to Deposit Account No. 02-2334 for any additional fees required under 37 C.F.R. §1.16 or under 37 C.F.R. §1.17; particularly extension of time fees.

Respectfully submitted,



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Enclosure: Version with Marking to Show Changes Made

Attorney Docket Number O 2000.551 US

Version with Marking to Show Changes Made

In the Claims

Claims 4-8 have been canceled.

The claims have been amended as follows:

1. (Amended) A [combination] pharmaceutical composition, comprising:

paracetamol or a non-steroidal anti-inflammatory drug [(NSAID)], or a pharmaceutically acceptable salt or solvate thereof, [and]

[another drug, characterized in that the other drug is] mirtazapine, or a pharmaceutically acceptable salt or solvate thereof, and

optionally in association with one or more pharmaceutically acceptable carriers.

2. (Amended) The [combination] pharmaceutical composition according to claim 1, [characterized in that the combination comprises a pharmaceutical composition which comprises both mirtazapine and paracetamol or an NSAID, optionally in association with one or ore pharmaceutically acceptable carriers] wherein said non-steroidal anti-inflammatory drug is selected from the group consisting of aceclofenac, antipyrine, acetylsalicylic acid, benoxaprofen, butibufen, caprofen, celecoxib, diclofenac, dipyrone, etodolac, flosulide, flurbiprofen, FR 140423, ibufenac, ibuprofen, indomethacin,

ketoprofen, ketorolac, lornoxicam, loxoprofen, lysine clonixinate, M-5011, meclofenamic acid, meloxicam, metiazinic acid, nabumetone, naproxen, NS-398, numesulide, oxyphenbutazone, D-penicillamine, phenylbutazone, piroxicam, pyrazolone, rofecoxib, salsalate, salicylate, SC-58236, SC58560, sulfasalasine, sulindac, tiaprofenic acid, tenidap, tenoxicam, tepoxalin, tolfenamic acid, tolmetin and zaltoprofen.

3. (Amended) The [combination] pharmaceutical composition according to claim [1 or] 2, [characterized in that the combination is with the NSAID] wherein said non-steroidal anti-inflammatory drug is ibupofen.

9. (Amended) A method for [the treatment of] treating a headache in a subject, [which method comprises treating] comprising:

administering to said subject an effective amount of mirtazapine in combination with paracetamol or [an NSAID] a non-steroidal anti-inflammatory drug.

10. (Amended) A method of [treatment of] treating a headache in a subject according to claim 9, [comprising administration of an amount of mirtazapine, charactereized in that] wherein the amount of mirtazapine is between 0.1 and 5 mg [mirtazapine].

11. (Amended) The method of [treatment of] treating a headache in a subject according to claim [3] 9, [characterized in that] wherein the headache is a tension-type headache.

12. (Amended) A patient pack for the treatment of a headache, comprising:

means for administration of metered dose units in combination with packaging material suitable for said dose units, [characterized in that] wherein the patient pack comprises mirtazapine, and [comprises] paracetamol or [an NSAID] a non-steroidal anti-inflammatory drug, and optionally, said packaging material is including means to help a recipient using the dose units most suitably for the treatment of a headache.

13. (Amended) [A] The patient pack according to claim 12, [for the treatment of headache comprising means for administration of metered dose units in combination with packaging material suitable for said dose units, characterized in that] wherein the dose units comprise pharmaceutical auxiliaries and mirtazapine in an amount between 0.1 and 5 mg [and optionally, said packaging material is including means to help a recipient using the dose units most suitably for the treatment headache].

Claims 14-17 have been added.

DRUG COMBINATION FOR THE TREATMENT OF HEADACHE COMPRISING A NON-STEROIDAL ANTI-INFLAMMATORY DRUG

The invention relates to a combination comprising paracetamol or a non-steroidal anti-inflammatory drug (NSAID), or a pharmaceutically acceptable salt or solvate thereof, and another drug, to a patient pack containing dose units comprising paracetamol or an NSAID or mirtazapine, and to a method of treatment of headache and related complaints.

Headache is a major cause of discomfort and a cause of a considerable amount of lost capacity for daily functioning. Many drugs are available to combat the complaint. Headache, in its severest form, is part of the complex of symptoms defining migraine. Other forms of headache occur episodically or periodically during menses or due to stress. The latter is known as tension-type headache. Analgesics, such as paracetamol, or non-steroidal anti-inflammatory drugs are usually used to combat the complaint. On many occurrences of headache the use of one drug is not sufficient and recourse is made to combinations of drugs in the field. For migraine such combinations are with analgesics, non-steroidal anti-inflammatory drugs (NSAID's), ergot alkaloids, antiserotonergics and anti-histamines. These combinations can have benefit due to additive effects of the components of the combination. More desirable is a truly synergistic effect of two drugs in the sense that the effect of the combination is superior over an additive effect of the effects of both drugs in an individual patient. There are only very few synergistic therapeutic drug interactions known which have found acceptance in the area of treatment of headache. Finding more effective drug therapies and more effective combinations is therefore an ongoing endeavour. It is the object of this invention to improve the means for treatment of headache and more specifically the means for treatment of tension-type headache. It is a further object of this invention to enhance the efficacy of common analgesics and an NSAID for the treatment tension-type headache.

Although combinations of paracetamol or NSAID's with other drugs are known (see for example van Gerven et al. British J Clinical Pharmacology volume 41, pages 475-481, 1996), it is found now that combining

paracetamol or an NSAID with the antidepressant drug mirtazapine has an extremely favourable effect in the treatment of headache.

This invention provides for a combination according to the opening paragraph, in which combination the other drug is mirtazapine, or a pharmaceutically acceptable salt or solvate thereof, optionally in association with one or more pharmaceutically acceptable carriers. More specifically, the invention provides for a combination comprising an amount of mirtazapine, or a pharmaceutically acceptable salt or solvate thereof, and an amount of paracetamol or an NSAID, or a pharmaceutically acceptable salt or solvate thereof, optionally in association with one or more pharmaceutically acceptable carriers, whereby the amount of paracetamol or the NSAID and the amount of mirtazapine are such that the effect of the combination is more favourable than the added effects of the amounts of each drug separately. Thus, the combination of paracetamol or an NSAID with mirtazapine truly has a synergistic interaction when used in the treatment of headache. As a consequence, the combined use of mirtazapine and an NSAID or paracetamol has better effects in more patients in comparison with the use of paracetamol or an NSAID alone. The better effect can reside in fewer side effects or a faster or more complete recovery in individual patients or in the overall result of the treatment of a group of patients. The preferred use of the combination will be in the treatment of tension-type headache.

Mirtazapine (Org 3770; disclosed in US patent 4,062,848) is a modern drug for the treatment of depression and anxiety with favourable side effect profiles and very low risks for a lethal overdose.

Non-steroidal anti-inflammatory drugs, which are the preferred drugs for combining with mirtazapine, are known from different chemical classes such as salicylics, pyrazolones or arylpropionics. Examples of specifically known NSAID are: aceclofenac, antipyrine, aspirin (acetylsalicylic acid), benoxaprofen, butibufen, carprofen, celecoxib, diclofenac, dipyrone, etodolac, flosulide, flurbiprofen, FR 140423, ibufenac, ibuprofen, indomethacin, ketoprofen, ketorolac, lornoxicam, loxoprofen, lysine

clonixinate, M-5011, meclofenamic acid, meloxicam, metiazinic acid, nabumetone, naproxen, NS-398, numesulide, oxyphenbutazone, D-penicillamine, phenylbutazone, piroxicam, pyrazolone, rofecoxib, salsalate, salicylate, SC-58236, SC-58560, sulfasalasine, sulindac, tiaprofenic acid, tenidap, tenoxicam, tepoxalin, tolfenamic acid, tolmetin and zaltoprofen. All these NSAIDS can be used in combination with mirtazapine with the desired improvement of effect. The combination of ibuprofen with mirtazapine is a more preferred combination of the invention.

NSAIDS are supposed to act as inhibitors of the enzyme cyclooxygenase (COX), involved in the biosynthesis of prostaglandins. There are two isoenzymes discovered, indicated as COX-1 and COX-2. It is the enzyme COX-2 that is mostly expressed in tissues with an inflammatory response. Those NSAID's, that inhibit COX-2 more selectively, are presumed to have fewer side effects in the general system, in particular the stomach. The NSAID's more selectively inhibiting COX-2 are carprofen, celecoxib, etodolac, flosulide, nabumetone, numesulide, rofecoxib and SC-58236.

Thus, the present invention concerns the administration of two different drugs from different pharmacological categories, one drug enhancing the therapeutic efficacy of the other drug in the treatment of headache.

It will be appreciated that mirtazapine and the NSAID's and the salts thereof may contain one or more centres of chirality and exist as stereoisomers including diastereomers and enantiomers. The present invention includes the aforementioned stereoisomers within its scope and each of the individual (R) and (S) enantiomers of the compounds and their salts, substantially free, i.e. associated with less than 5%, preferably less than 2%, in particular less than 1% of the other enantiomer and mixtures of such enantiomers in any proportions including racemic mixtures containing substantially equal amounts of the enantiomers.

The following specifications of the terms used above serve to clarify better

what is provided by this invention.

The drug name mirtazapine also refers to the individual (R) and (S) enantiomers of mirtazapine. These can be used as their salts, substantially free of the other enantiomer or as mixtures of such enantiomers in any proportions.

Unless otherwise stated all amounts of the active components refer to the weights of mirtazapine as base or of paracetamol or the NSAID's as base or acid without inclusion of an amount of crystal water or added acid or base to form an addition salt. According to the terminology in this description paracetamol or the NSAID's, as at least one component, and mirtazapine, as at least a second component, are the active ingredients or active components of the combination.

Pharmaceutically acceptable addition salts are those that can be obtained with, for example, hydrochloric, fumaric, maleic, citric, succinic acid or sodium or potassium hydroxyde.

The terms pharmaceutically acceptable carriers and excipients refer to those substances known in the art to be allowable as filler or carrier material in pills, tablets, capsules etc. The substances are usually approved for this purpose by health-care authorities and are inactive as pharmacological agents. A compilation of pharmaceutically acceptable carriers and excipients can be found in the Handbook of Pharmaceutical excipients (2nd edition edited by A. Wade and P.J. Weller; Published by the American Pharmaceutical Association, Washington and The Pharmaceutical Press, London in 1994). Specifically, lactose, starch, cellulose derivatives and the like, or mixtures thereof, can be used as carriers for the active components of the combination according to this invention.

The term combination refers to any presentation form in which the intention for use of mirtazapine in combination with paracetamol or an NSAID can be recognised. Such combinations with mirtazapine may in this description also be referred to as combinations according to the

invention.

It will be appreciated that the compounds of the combination may be administered concomitantly, either in the same or different pharmaceutical formulation or sequentially. If there is sequential administration, the delay in administering the second (or additional) active ingredient should not be such as to lose the benefit of the efficacious effect of the combination of the active ingredients. A minimum requirement for a combination according to this description is that the combination should be intended for combined use with the benefit of the efficacious effect of the combination of the active ingredients. The intended use of a combination can be inferred by facilities, provisions, adaptations and/or other means to help using the combination according to the invention. For example, a combination can be made suitable by adding instructions or aids or even determinants for the combined use. Determinants for the combined use can, for example, reside in the properties of a dispenser of dosage units of the active ingredients of the combination. The active ingredients can thus be in separate dosage units, but still the combination can have a determinant inducing the use of the dosage units of the combination in a predetermined sequence and/or at pre-determined times by the properties of the dispenser. A preferred determinant for combined use is of course the formulation of both the active components of the combination in one pharmaceutical composition.

Thus according to one aspect, the present invention provides a pharmaceutical composition, comprising mirtazapine, or a pharmaceutically acceptable salt or solvate thereof, and comprising paracetamol or an NSAID, or a pharmaceutically acceptable salt or solvate thereof.

There are several types of headache complaints in people. Tension-type headache is the most common one among this group of complaints. The characteristic is that the pain is typically pressing or tightening in quality, of mild to moderate intensity, bilateral in location and does not worsen with routine physical activity. Nausea is absent, but bothersome hypersensitivity to light and noise may occur. Tension-type headache is preferably selected to be treated with the combination according to this

invention. There are two types of tension-type headaches: Episodic tension-type headache and chronic tension-type headache. The first is characterised by recurrent episodes of headache lasting minutes to days. Chronic tension-type headache is characterised by presence for at least 15 days per month for at least 6 months.

The subject amenable for a treatment made available by this invention is a human person. Men and women often respond differently to drug treatment and suffer differently in nature, frequency and severity from headache. Also, there are differences in treatment methods for persons with headache among different age groups. The elderly, adolescents or postmenopausal age groups have different needs for treatment. Such differential factors are to be taken into account in selecting the treatment of this invention and in selecting the exact dose of the active ingredients for the treatment.

For the use of the combination of the present invention it should provide the active ingredients such that effective amounts for treatment are made available. The amount of a combination of mirtazapine (or a pharmaceutically acceptable salt or solvate thereof) and paracetamol or an NSAID (or a pharmaceutically acceptable salt or solvate thereof), required to produce the efficacious effects will, of course, vary and is ultimately at the discretion of the medical practitioner. The factors to be considered include the route of administration and nature of the formulation, the recipient's body weight, age and general condition and the nature and severity of the headache to be treated. In general, parenteral administration requires lower dosages than other methods of administration, which are more dependent upon absorption.

Dosages of paracetamol or NSAIDS for carrying out the invention are in the range generally recommended a particular compound. For example, for ibuprofen the recommended dose is within the range between 10 and 400 mg per recipient per day, with a dosage in the range between 100 and 300 mg as the more preferred range within which to select a dose for the combination. The recipient is the subject receiving the active ingredients of the combination for treatment of headache.

Dosages for mirtazapine generally will be within the range of 0.1 to 60 mg per recipient per day. However, the daily dosages to a recipient are preferably between 0.1 and 10 mg and more preferably lower than 5 mg.

Since the dose of mirtazapine suitable for obtaining the synergistic effect with paracetamol or an NSAID on headache is far below the amount in currently available dosing units, it is another aspect of the invention that it discloses the use of mirtazapine for the manufacture of a medicament for the treatment of headache, which treatment comprises the administration of mirtazapine with a unit treatment dose comprising more than 0.1 and less than 5 mg mirtazapine, which in other words is a unit treatment dose (within the range) between 0.1 and 5 mg mirtazapine.

While it is possible for the active ingredients of the combination to be administered as the raw chemical it is preferable to present them as a pharmaceutical composition, also referred to in this context as pharmaceutical formulation. Suitable compositions include those suitable for oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. Pharmaceutical compositions according to the present invention comprise mirtazapine or paracetamol or an NSAID or a combination thereof comprising mirtazapine, together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. The present invention further provides compositions according to the invention for use in therapy of headache. Furthermore, the invention includes the use of mirtazapine and paracetamol or an NSAID in the manufacture of a medicament comprising mirtazapine and paracetamol or an NSAID with improved efficacy for therapy of headache. This medicament has an enhanced effect or fewer side effects in comparison to each drug alone. The preferred use of the medicament will be for the treatment of tension-type headache. The invention includes as well the use of mirtazapine and paracetamol or an NSAID in the manufacture of medicaments for administration in combination (either concomitantly or sequentially) respectively with paracetamol or an

NSAID, or with mirtazapine, for the treatment of headache.

An important aspect of the present invention is that it provides a method for the treatment of an individual of a vertebrate species, for example, a mammal including a human patient, suffering from headache, which method of treatment comprises administering an effective amount of mirtazapine in combination with paracetamol or an NSAID. The desired daily doses for a treatment is preferably presented as a single dose or in two, or three sub-doses administered at appropriate intervals throughout the day. In practice this means among others to provide dosage units comprising mirtazapine and dosage units comprising paracetamol or an NSAID in a combination or to provide dosage units comprising mirtazapine and paracetamol or an NSAID for administration to a recipient or intake by a recipient for treatment.

Thus, in one embodiment of the invention a mixture of mirtazapine and paracetamol or an NSAID may be presented as a pharmaceutical formulation in dosage unit form, for example, administered in the form of a tablet, pill, capsule and the like. Such dosage forms are known in the art, e.g. as described in the standard reference, Gennaro et al., Remington's Pharmaceutical Sciences, (18th ed., Mack Publishing Company, 1990, see especially Part 8: Pharmaceutical Preparations and Their Manufacture). By means of pharmaceutically suitable liquids the compounds can also be applied as an injection preparation in the form of a solution, suspension, emulsion, or as a spray, e.g. a nasal spray.

For the preparation of pharmaceutical compositions and more specifically dosing units, the present invention further includes a process for the preparation of a pharmaceutical formulation comprising mirtazapine and paracetamol or an NSAID, which process comprises bringing an amount of mirtazapine (or a pharmaceutically acceptable salt thereof) and amount of paracetamol or an NSAID (or a pharmaceutically acceptable salt thereof) into association with one or more pharmaceutical excipients.

More commonly these days pharmaceutical formulations are prescribed to the patient in "patient packs" containing a number dosing units or other means for administration of metered dose units for use during a

distinct treatment period in a single package, usually a blister pack. Patient packs have an advantage over traditional prescriptions, where a pharmacist divides a patients supply of a pharmaceutical from a bulk supply, in that the patient always has access to the package insert contained in the patient pack, normally missing in traditional prescriptions. The inclusion of a package insert has been shown to improve patient compliance with the physician's instructions. Thus, the invention further includes a pharmaceutical formulation, as herein before described, in combination with packaging material suitable for said formulations. In such a patient pack the intended use of a formulation for the combination treatment of headache can be inferred by instructions, facilities, provisions, adaptations and/or other means to help using the formulation most suitably for the treatment. Such measures make a patient pack specifically suitable for and adapted for use for treatment with the combination of the present invention.

Specifically, a further embodiment includes a package containing separate dose units, one or more of which containing mirtazapine or a pharmaceutically acceptable salt thereof and one or more of which containing paracetamol or an NSAID or a pharmaceutically acceptable salt thereof. A package contains enough tablets, capsules or the like to treat a patient for a pre-determined period of time, for instance for 1 week.

Thus, the invention provides a patient pack for the treatment of headache comprising means for administration of metered dose units in combination with packaging material suitable for said dose units, which patient pack comprises mirtazapine and paracetamol or an NSAID and optionally, said packaging material is including means to help a recipient using the dose units most suitably for the treatment headache.

Furthermore, the invention provides a patient pack for the treatment of headache comprising means for administration of metered dose units in combination with packaging material suitable for said dose units, which dose units comprise pharmaceutical auxiliaries and mirtazapine in an amount between 0.1 and 5 mg and optionally, said packaging material is including means to help a recipient using the dose units most suitably for the treatment headache.

The compositions (formulations) according to this invention may be prepared by any methods well known in the art of pharmacy, for example, using methods such as those described in Gennaro et al., Remington's Pharmaceutical Sciences (18th ed., Mack Publishing Company, 1990, see especially Part 8: Pharmaceutical Preparations and their Manufacture). Such methods include the step of bringing into association an active ingredient with a carrier, which constitutes one or more accessory ingredients. Such accessory ingredients include those conventional in the art, such as, fillers, binders, diluents, disintegrants, lubricants, colorants, flavouring agents and wetting agents.

Formulations suitable for oral administration may be presented as discrete units such as pills, tablets or capsules each containing a predetermined amount of active ingredient(s); as a powder or granules; as a solution or suspension. The active ingredient(s) may also be present as a bolus or paste, or may be contained within liposomes.

Formulations for rectal administration may be presented as a suppository or enema.

For parenteral administration, suitable formulations include aqueous and non-aqueous sterile injection. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed vials and ampoules, and may be stored in a freeze dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example, water prior to use.

Formulations suitable for administration by nasal inhalation include fine dusts or mists, which may be generated by means of metered, dose pressurised aerosols, nebulisers or insufflators.

For making dose units, e.g. tablets, the use of conventional additives such as fillers, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used. Suitable

amounts of active ingredients are, for example, a tablet comprising 0.1 to 60 mg of mirtazapine and typically 0.5 to 500 mg of an NSAID. In a specific example, a tablet comprising 4 mg of mirtazapine and 200 mg of ibuprofen is obtained.

Mirtazapine may be prepared using the method described in US 4,062,848 which is incorporated herein by reference.
Paracetamol and an NSAID may be prepared by any method known in the art. Typically the mentioned compounds are prepared by the methods described in patents concerning these compounds. The contents of these documents are incorporated herein by reference.

The invention is further illustrated by the following examples.

Example 1

Mirtazapine is formulated in dosing units containing 0.5 mg, 1.5 mg and 4.5 mg mirtazapine.
The dosing units containing 0.5 mg (as tablets) have the composition as indicated in table 1:

Table 1

	Per tablet	Per batch
Tablet excipients	in mg	In gram
Mirtazapine	0.5	7.7
Corn starch	6.5	100.0
Hydroxypropylcellulose	1.3	20.0
Magnesium stearate	0.4875	7.5
Aerosil	0.975	15.0
Lactose 200 M	to 65 mg	To 1000 gram

For preparation of tablets a 1000 g granulate batch with the composition indicated in table 1 was prepared by premixing the complete amount of mirtazapine (base) with 100 gram of lactose 200 M in a 1 litre glass container for 10 minutes on a Turbula mixer at 22 rotations per minute (rpm). The mixture is sieved through a 150 µm sieve before and after

which a further 20 g of lactose 200 M is added. Granulation was performed in a high shear mixer granulator with the rest of the lactose, cornstarch and hydroxypropyl-cellulose. The granulate was dried in a tray vacuum cabinet, classified with a conical screen mill and mixed with aerosil and magnesium stearate. The 65 mg tablets were compressed with a diameter of 5 mm and a radius of convexity of 7.5 mm. Tablets with 1.5 and 4.5 mg mirtazapine were prepared similarly whereby the quantity of lactose was adapted in order to compensate for the increased quantity of mirtazapine.

Dosing units containing, 1.5 mg and 4.5 mg mirtazapine were prepared analogously with compensatory reduction of the amount of lactose 200 Mesh.

Example 2

A 55 year old female subject, episodically suffering from tension-type headache was unresponsive to treatment with ibuprofen. This drug did not relieve the symptoms when given at the generally recommended dose of 200 mg, nor at the elevated dose of 400 mg.

Addition of 3-4 mg mirtazapine (Remeron®) to 200 mg of ibuprofen, however, results in complete disappearance of the headache. Mirtazapine alone has no effect. It is concluded that in this subject acute treatment of tension-type headache with a combination of a normal dose of ibuprofen and a low dose of mirtazapine is successful and that ibuprofen and mirtazapine act synergistically since neither drug alone has the desired effect.

Claims

1. A combination comprising paracetamol or a non-steroidal anti-inflammatory drug (NSAID), or a pharmaceutically acceptable salt or solvate thereof, and another drug, characterised in that the other drug is mirtazapine, or a pharmaceutically acceptable salt or solvate thereof, optionally in association with one or more pharmaceutically acceptable carriers.

2. The combination according to claim 1, characterised in that the combination comprises a pharmaceutical composition which comprises both mirtazapine and paracetamol or an NSAID, optionally in association with one or more pharmaceutically acceptable carriers.

3. The combination according to claim 1 or 2, characterised in that the combination is with the NSAID ibuprofen.

4. Use of mirtazapine in combination with paracetamol or an NSAID in the manufacture of a medicament for the treatment of headache.

5. Use of mirtazapine in the manufacture of a medicament, characterised in that the medicament is for the treatment of headache, which treatment comprises administration of mirtazapine in combination with paracetamol or an NSAID

6. The use of mirtazapine for the manufacture of a medicament, characterised in that the medicament is for the treatment of headache comprising the administration of mirtazapine with a unit treatment dose comprising between 0.1 and 5 mg mirtazapine.

7. Use of paracetamol or an NSAID in the manufacture of a medicament for the treatment of headache, characterised in that the medicament is for administration in combination with mirtazapine.

8. The uses according to any one of claim 4 to 8, characterised in that the headache is tension-type headache.

9. A method for the treatment of headache in a subject which method comprises treating said subject with an effective amount of mirtazapine in combination with paracetamol or an NSAID.

10. A method of treatment of headache in a subject comprising the administration of an amount of mirtazapine, characterised in that the amount is between 0.1 and 5 mg mirtazapine.

11. The method of treatment according to claim 3, characterised in that the headache is tension-type headache.

12. A patient pack for the treatment of headache comprising means for administration of metered dose units in combination with packaging material suitable for said dose units, characterised in that the patient pack comprises mirtazapine and comprises paracetamol or an NSAID and optionally, said packaging material is including means to help a recipient using the dose units most suitably for the treatment headache.

13. A patient pack for the treatment of headache comprising means for administration of metered dose units in combination with packaging material suitable for said dose units, characterised in that the dose units comprise pharmaceutical auxiliaries and mirtazapine in an amount between 0.1 and 5 mg and optionally, said packaging material is including means to help a recipient using the dose units most suitably for the treatment headache.

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(54) Title: DRUG COMBINATION FOR THE TREATMENT OF HEADACHE COMPRISING A NON-STEROIDAL ANTI-INFLAMMATORY DRUG

(57) Abstract: The invention relates to a combination comprising paracetamol or a non-steroidal anti-inflammatory drug (NSAID), or a pharmaceutically acceptable salt or solvate thereof, and another drug, in which combination the other drug is mirtazapine, or a pharmaceutically acceptable salt or solvate thereof, optionally in association with one or more pharmaceutically acceptable carriers, whereby paracetamol or an NSAID and mirtazapine are present in the combination in such amounts that the effect of the composition is more favourable than the added effects of the amounts of each drug separately. This combination can be used in the treatment of headache, whereby the invention also provides for a new method of treatment of headache.

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

2000.551 US

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original first and joint inventor (if plural names are listed below) of the subject matter for which a patent is sought on the invention entitled:

DRUG COMBINATION FOR THE TREATMENT OF HEADACHE COMPRISING MIRTAZAPINE AND PARACETAMOL OR A NON-STEROIDAL ANTI-INFLAMMATORY DRUG

the specification of which
[CHECK ONE]

[ ] is attached hereto

[ ] was filed on _____ as Application Serial No. _____ and was amended on _____
[if applicable]

[X] as filed under the Patent Cooperation Treaty on ***04/04/2001*** Serial ***EP01/04069*** , The United States of America being designated.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claim(s), as amended by any amendment referred to above.

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I hereby claim foreign priority benefits under Title 35, United States Code, Section 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign applications(s) for patent or inventor's certificate having a filing date before that of the application(s) on which priority is claimed:

Prior Foreign Application(s)			Priority claimed
00201239.1	*EP*	*05/04/2000*	X Yes ____ No
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_____	_____	_____	____ Yes ____ No
Number	Country	Day/Month/Year filed	
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Number	Country	Day/Month/Year filed	

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application(s) in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose to the patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which

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(2) And I hereby appoint as principal attorney, William M. Blackstone, Registration No. 29,172 and Michael G. Sullivan, Registration No. 35,377.

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1-00

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